R E M A R K S

It is respectfully requested that the above amendments be entered pursuant to the provisions of 37 C.F.R. §1.116(a); that this application be reconsidered in view of the above amendments and the following remarks; and that all of the claims remaining in this application be allowed.

Interview

At the outset, the undersigned wishes to thank Examiners Weber and Wityshyn for the courtesies extended to himself and joint inventors Steele and Burton during the interview conducted for this application on December 11, 1996 via videoconferencing. The substance of this interview is accurately reflected in the Interview Summary provided by the Examiner which substance is elaborated upon in the remarks below.

Amendments

The specification has been amended at page 3, line 22, at page 5, line 21, and page 13, line 3, to correct obvious grammatical errors.

Claims 1 and 16 have been amended to also correct a grammatical error and to recite that the protein/peptide binds to the resin at a pH of from 5 to 9. Support for this latter amendment is found in Applicants' specification at, for example, page 29, lines 24-29.

Applicants submit that the above amendments either conform the claims to matter of form required by the USPTO and/or place the claims in better form for appeal and, accordingly, their entry under 37 C.F.R. §1.116(a) is proper. Entry of these amendments is earnestly requested.

Objection/Rejection Under 35 U.S.C. §112

The specification stands objected to and Claims 1-5 and 7-23 stand rejected under 35 U.S.C. §112, first paragraph, because the recitation that peptide/protein binding is from pH 5 or more is not supported by the specification in the "or more" language and is allegedly new matter. This objection/rejection has been obviated by the amendments to Claims 1 and 16 which now recite that such binding occurs at a pH of from 5 to 9 which is clearly supported by Applicants' specification. This objection/rejection is therefore moot and withdrawal of this objection/rejection is earnestly solicited.

Rejection Under 35 U.S.C. §103

Claims 1-23 stand finally rejected under 35 U.S.C. §103 over Sasaki, et al., *J. Biochem.*, 86:1537-1548 (1979) ("Sasaki '79") or Sasaki, et al., *J. Biochem.*, 91:1551-1561 (1982) ("Sasaki '82") in view of Kasche, et al., *J. Chromatogr.*, 510:149-154 (1990) ("Kasche"), Teichberg, *J. Chromatogr.*, 510:49-57 (1990) ("Teichberg") and Jost, et al., *Biochem. Biophys. Acta*, 362:75-82 (1974) ("Jost"). For the following reasons, this rejection is traversed.

As noted during the interview, Applicants' claimed invention is directed to a *resin/protein complex*[1] which, accordingly, infers that the claims covering this invention are composition claims. In these complexes, the resin is characterized, in part, as being electrostatically uncharged when the target protein is bound to the resin at a pH of from 5 to 9 and is further characterized as being electrostatically charged at the pH of desorption. Still further, Applicants' claimed invention recites that the pH where the protein or peptide is bound to the resin is different than the pH where the protein or peptide is desorbed from the resin.

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[1] The term "protein" in resin/protein complexes is intended to cover both proteins and peptides. Moreover, as noted during the interview, Applicants no longer rely upon the Becker declaration as it relates to either Sasaki article and this declaration should be disregarded.

Among other factors, Applicants' claimed invention is based on the discovery that resin-protein complexes wherein the resin is electrostatically uncharged at the pH where the protein or peptide is bound to the resin provides, in part, for an efficient binding of the protein to the resin for example from an aqueous media having either high or low ionic strength. Moreover, a binding pH of from 5 to 9 provides for resin/protein complexes which avoid the use of strong acidic/basic conditions which can denature some proteins. See, for example, page 29, lines 24 et seq., of Applicants' specification.

Applicants maintain that this §103 rejection of Claims 1-23 over the cited references is in error because these references, either alone or in combination do not teach or suggest Applicants' now claimed invention.

Initially, Applicants note that the test for non-obviousness articulated by the Court of Appeals for the Federal Circuit in *In re Vaeck* requires consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition; and (2) whether the prior art would also have provide a reasonable expectation of success to such a skilled artisan. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

This requirement goes to the question of motivation, and refers to a well established holding from earlier case law that there must be some logical reason at the time of the invention for combining the references along the lines of the invention; otherwise the use of the teachings as evidence of non-obviousness will entail prohibited hindsight. *Ex parte Stauber and Eberle*, 208 U.S.P.Q. 945, 946 (Bd. App. 1980).

As a further elaboration noted during the interview, the claims of this invention are composition claims and, by necessity, the patentability of these claims are evaluated by whether these compositions are *prima facie* obvious over prior art compositions taking

into account issues such as the similarity of these compositions to the prior art. *In re Deuel*, 34 USPQ2d 1210 (Fed. Cir. 1995).

Based on the above criteria, Applicants maintain that these cited prior art references, either alone or in combination, fail to achieve a *prima facie* case of obviousness against their claimed compositions.

Specifically, the cited Sasaki articles are not pertinent to the now claimed invention because these articles fail to disclose resin/protein compositions where the resin, containing ionizable functionality, is electrostatically uncharged at physiological pH's of from 5 to 9 while having protein bound thereto. As noted during the interview, Sasaki's teachings clearly lead to the conclusion that the ionizable Amberlite CG-50 resins employed therein are charged at any pH within this range because Sasaki states that a pH of 4.5 or less is required to completely protonate the carboxyl groups of the resins. Accordingly, at a pH of 5 or more, Sasaki's Amberlite CG-50 resins would carry anionic charge. Sasaki himself recognized this limitation at page 1561 of his 1982 article where he states that:

> "However, hydrophobic-ionic chromatography with Amberlite CG-50 has the disadvantage that a pH as acidic as 4.5 is required in the process of adsorption".

Moreover, neither Sasaki article discloses any ionizable ligands which would be electrostatically uncharged at a physiological pH range of from 5 to 9 and bind proteins but, at best, Sasaki (1982) merely discloses the possibility of absorbents carrying alkaline groups. Accordingly, by themselves, these articles fail to provide any motivation to the skilled artisan to arrive at the composition of the now claimed invention.

The secondary references relied upon in this rejection fail to cure the deficiencies of the Sasaki articles because these secondary references each employ resins requiring electrostatic charge during protein recovery.

Specifically, the Kasche reference shows binding of proteins to a resin which, under the conditions employed by Kasche, contain significant positive charge and, accordingly, Kasche cannot disclose the resin/protein complexes of this invention. Specifically, Kasche's Figure 2 illustrates the charge density of phenylbutylamine (PBA) Eupergit resin from about pH 2-10 in the absence of bound protein. As shown in this figure, the resin contains substantial electrostatic charge at pH's of about 8 or less. However, Kasche's experimental section recites in the second and third paragraphs of page 151 and in Figure 3 that enzyme (e.g., penicillin amidase from *E. coli* homogenates) was contacted with the PBA-Eupergit resin at pH 7.5 and Kasche's Figure 1 recites a contacting the resin to an enzyme containing solution at pH 7. In each case, the PBA-Eupergit resin carries a significant electrostatic charge. In point of fact, Kasche's statement in the bridging sentence between pages 152 and 153 that:

> "...hydrophobic interactions cause the adsorption, and ... charge-charge repulsions on the support limit the adsorption capacity"

supports Kasche's recognition that his supports carry charge at the pH of absorption. Significantly, Kasche does not suggest that one should avoid this charge by adjusting the pH to a value where the resin is electrostatically uncharged.

As to the Teichberg and Jost references, these are irrelevant to the claims in this application because neither reference is addressing the problem solved by this invention.

Specifically, Teichberg is concerned with affinity-repulsion chromatography whereas Applicants' methods are not directed to affinity chromatography. Further, and

more to the point, Teichberg recites at page 54 et seq. that the matrices employed therein are charged when the protein is bound to the resin. Such a requirement is contrary to Applicants' claimed invention.

Jost is concerned with determining whether binding of negatively charged proteins such as ovalbumin and β-lactoglobulin is due to hydrophobic or electrostatic interactions. In any event and, again, more to the point, Jost similarly discloses the necessity of charged groups (i.e., positively charged groups) in his resins to effect protein recovery. Specifically, Jost compares resins conventionally charged at physiological pH (i.e., CNBr activated agarose derivatized with alkyl- and arylamines) versus resins which apparently are uncharged at physiological pH but having one or two dissociation ranges (agarose derivatized with alkyl or aryl hydrazides). Jost states at page 75 (column 2) that:

> "The experiments presented in this paper describe the adsorption of ovalbumin, α-lactalbumin, and leucine aminopeptidase (EC 3.4.1.1) to alkyl- and arylamino-agaroses and demonstrate the abolishment of such binding in structurally closely related uncharged agarose derivatives, prepared from the corresponding alkyl or aryl hydrazides."

The only protein which bound to the uncharged agarose derivatives of Jost was bovine serum albumin (BSA) which Jost recites as being "bound almost irreversibly" to this resin. In point of fact, Jost describes that attempted "[d]esorption [of the BSA] with 1 M NaCl was unsuccessful". See, for example, the first five lines under Table I of Jost. However, Jost describes that the use of positively charged resin permits binding and recovery of BSA. See, e.g., Table 1 of Jost. Accordingly, Jost teaches that in the absence of charged groups on the resin, two proteins did not bind to the resin and a third (BSA) bound apparently irreversibly to the resin thus preventing recovery of the BSA. As is apparent, irreversible binding in this third resin does not lend itself to protein recovery from an aqueous mixture.

In view of the above, each of the cited secondary references fails to teach the desirability of employing an ionizable but electrostatically uncharged resin in the physiological pH range of 5 to 9 during protein recovery and, hence, cannot cure the deficiencies of Sasaki ('79 and/or '82).

Accordingly, the combination of references provided in this rejection simply fails to suggest to one skilled in the art the desirability of making the compositions of this invention. Nor do these references, either alone or in combination, provide a reasonable expectation of success to a skilled artisan that the modifications necessary to either Sasaki article to arrive at the claimed invention would be successful in effecting protein recovery. Absent such suggestion and reasonable expectation, this rejection is in error. *In re Vaeck, supra.* Withdrawal of this rejection is requested.

While Applicants submit that this application is now in condition for allowance, a Notice of Appeal is enclosed to prevent the unintended abandonment of this application.

Respectfully submitted,

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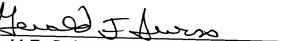
By: 

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Date: February 19, 1997